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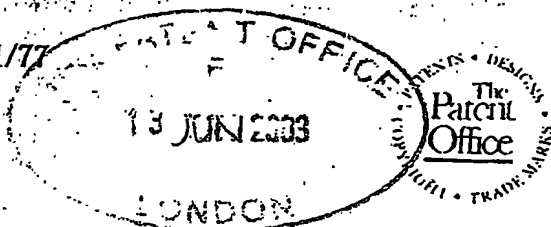
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16JUN03 E815022-1 D02639  
P01/7700 0.00-0313772.6

# Request for grant of a patent

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13 JUN 2003

1. Your reference

2. Patent application number

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T1633PV

0313772.6

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Merck Sharp & Dohme Limited  
Hertford Road, Hoddesdon  
Hertfordshire EN11 9BU  
United Kingdom  
00597799001

Patents ADP number (if you know it)

United Kingdom

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

Therapeutic treatment

Name of your agent (if you have one)

Dr. G. M. Buchan

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

Merck & Co., Inc.  
European Patent Department  
Terlings Park  
Eastwick Road  
Harlow  
Essex CM20 2QR

Patents ADP number (if you know it)

4448791001

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Country

Priority application number  
(if you know it)

Date of filing  
(day / month / year)

If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing  
(day / month / year)

Is a statement of inventorship and of right of grant of a patent required in support of this request? (Answer 'Yes' if:

Yes

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## Patents Form 1/77

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Request for preliminary examination and search (Patents Form 9/77)	-
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11. I/We request the grant of a patent on the basis of this application.

Signature



Date 13 June 2003

Dr. G. M. Buchan

12. Name and daytime telephone number of person to contact in the United Kingdom

Dr. G. M. Buchan

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### THERAPEUTIC TREATMENT

This invention relates to the use of methods and materials for therapeutic treatment of the human body. In particular, it provides methods of treating diseases associated with the deposition of  $\beta$ -amyloid in the brain, such as Alzheimer's disease, or of preventing or delaying the onset of dementia associated with such diseases.

Alzheimer's disease (AD) is the most prevalent form of dementia. Its diagnosis is described in the Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> ed., published by the American Psychiatric Association (DSM-IV). It is a neurodegenerative disorder, clinically characterized by progressive loss of memory and general cognitive function, and pathologically characterized by the deposition of extracellular proteinaceous plaques in the cortical and associative brain regions of sufferers. These plaques mainly comprise fibrillar aggregates of  $\beta$ -amyloid peptide ( $A\beta$ ).  $A\beta$  is formed from amyloid precursor protein (APP) via separate intracellular proteolytic events involving the enzymes  $\beta$ -secretase and  $\gamma$ -secretase. Variability in the site of the proteolysis mediated by  $\gamma$ -secretase results in  $A\beta$  of varying chain length, e.g.  $A\beta$  1-38, 1-40 and 1-42. After secretion into the extracellular medium, the initially-soluble  $A\beta$  forms aggregates which ultimately result in the insoluble deposits and dense neuritic plaques which are the pathological characteristics of AD.

Other dementing conditions associated with deposition of  $A\beta$  in the brain include cerebral amyloid angiopathy, multi-infarct dementia, dementia pugilistica and Down syndrome.

Various interventions in the plaque-forming process have been proposed as therapeutic treatments for AD (see, for example, Hardy and Selkoe, *Science*, 297 (2002), 353-6). One such method of treatment that has been proposed is that of blocking or attenuating the production of  $A\beta$ , for example by inhibition of  $\beta$ - or  $\gamma$ -secretase. Compounds which inhibit  $\gamma$ -secretase are disclosed in WO 01/53255, WO 01/66564, WO 01/70677, WO

01/90084, WO 01/77144, WO 02/30912, WO 02/36555, WO 02/081435, WO  
 02/081433, WO 03/018543, WO 03/013506, WO 03/013527 and WO  
 03/014075. Compounds which inhibit  $\beta$ -secretase are disclosed in WO  
 03/037325, WO 03/030886, WO 03/006013, WO 03/006021, WO 03/006423,  
 5 WO 03/006453, WO 02/002122, WO 01/70672, WO 02/02505, WO  
 02/02506, WO 02/02512, WO 02/02520, WO 02/098849 and WO 02/100820.  
 Other compounds which inhibit the formation or release of  $A\beta$  include  
 those disclosed in WO 98/28268, WO 02/47671, WO 99/67221, WO  
 01/34639, WO 01/34571, WO 00/07995, WO 00/38618, WO 01/92235, WO  
 10 01/77086, WO 01/74784, WO 01/74796, WO 01/74783, WO 01/60826, WO  
 01/19797, WO 01/27108, WO 01/27091, WO 00/50391, WO 02/057252, US  
 2002/0025955 and US2002/0022621.

It has also been reported that inhibition of glycogen synthase  
 kinase-3 (GSK-3), in particular inhibition of GSK-3 $\alpha$ , can block the  
 15 production of  $A\beta$  (see Phiel et al, *Nature*, 423 (2003), 435-9).

Another such method of treatment that has been proposed is that of  
 modulation of the action of  $\gamma$ -secretase so as to selectively attenuate the  
 production of  $A\beta$  (1-42). This results in preferential secretion of the  
 shorter chain isoforms of  $A\beta$ , which are believed to have a reduced  
 20 propensity for self-aggregation and plaque formation, and hence are more  
 easily cleared from the brain, and/or are less neurotoxic. Compounds  
 showing this effect include certain non-steroidal antiinflammatory drugs  
 (NSAIDs) and their analogues (see WO 01/78721 and US 2002/0128319).  
 Compounds which modulate the activity of PPAR $\alpha$  and/or PPAR $\delta$  are also  
 25 reported to have the effect of lowering  $A\beta$  1-42 (WO 02/100836). NSAID  
 derivatives capable of releasing nitric oxide have been reported to show  
 improved anti-neuroinflammatory effects and/or to reduce intracerebral  
 $A\beta$  deposition in animal models (WO 02/092072; Jantzen et al, *J.*  
*Neuroscience*, 22 (2002), 226-54).

30 Another such method of treatment that has been proposed is that of  
 administering a compound which blocks the aggregation of  $A\beta$ .

Compounds having this property include chelating agents such as clioquinol (Gouras and Beal, *Neuron*, **30** (2001), 641-2) and the compounds disclosed in WO 99/16741, in particular that known as DP-109

(Kalendarev et al, *J. Pharm. Biomed. Anal.*, **24** (2001), 967-75). Other

5 inhibitors of A $\beta$  aggregation include the compounds disclosed in WO 96/28471, WO 98/08868 and WO 00/052048, including the compound known as Apan<sup>TM</sup> (Praecis), WO 00/064420, WO 03/017994, WO 99/59571 and the compound known as Alzhemed<sup>TM</sup> (Neurochem), WO 00/149281 and the compositions known as PTI-777 and PTI-00703 (ProteoTech), WO  
10 96/39834, WO 01/83425, WO 01/55093, WO 00/76988, WO 00/76987, WO 00/76969, WO 00/76489, WO 97/26919, WO 97/16194, and WO 97/16191.

Another such method of treatment that has been proposed is that of administering an antibody which selectively binds to A $\beta$ . Such antibodies may be brain-penetrant and capable of binding to insoluble A $\beta$ , as  
15 described in WO 99/60024 and WO 00/72880 for example. Alternatively, such antibodies may be capable of sequestering soluble A $\beta$  from biological fluids, without necessarily being brain-penetrant. It is believed that in these circumstances the removal of unbound A $\beta$  from the serum increases the relevant concentration gradient between brain and serum, causing an  
20 efflux of A $\beta$  from the brain to the serum. This approach is described in WO 03/016466, WO 03/016467, WO 03/015691 and WO 01/62801.

Growth hormone has been proposed for use in treatment of AD. Thus, US 4,902,680 advocates the administration of growth hormone to patients in the advanced stages of AD, while WO 00/13650 discloses that  
25 increased levels of growth hormone in the brain provide a neuroprotective effect, and in particular can rescue neurons that would otherwise die as a result of an insult such as that associated with a neurodegenerative disease such as AD. The injection of growth hormone into the brain is contemplated.

30 Growth hormone secretagogues (GHSs) are compounds which, when administered to an animal (such as a human), stimulate or increase the

release of endogenous growth hormone in the animal. Their mode of action and clinical utilities are reviewed by Ankersen et al, *Drug Discovery Today*, 4 (1999), 497-506; Casanueva and Dieguez, *TEM*, 10 (1999), 30-8; Smith et al, *ibid.*, 10 (1999), 128-35; Betancourt and Smith, *J. Anti-Aging Med.*, 5 (2002), 63-72; and Ghigo et al, *ibid.*, 5 (2002), 345-56, but there is no mention of treating AD or any other neurodegenerative condition.

Patents and patent applications disclosing compounds which are GHSs include US 5,767,124, US 5,536,716, WO 94/13696, EP 0615977B, US 5,578,593; WO 01/04119, WO 98/25897, WO 98/10653, WO 97/36873, WO 97/34604, WO 97/15574, WO 97/11697, WO 96/32943, WO 96/13265, WO 96/02530, WO 95/34311, WO 95/14666, WO 95/13069, WO 94/19367, WO 94/05634 and WO 92/16524 (all assigned to Merck & Co., Inc.); EP 1002802A, EP 0995748A, WO 98/58948, WO 98/58947 and WO 97/24369 (all assigned to Pfizer Inc.); WO 01/34593, WO 00/26252, WO 00/01726, WO 99/64456, WO 99/58501, WO 99/36431, WO 98/58950, WO 98/08492, WO 98/03473, WO 97/40071, WO 97/40023, WO 97/23508, WO 97/00894, WO 96/24587, WO 96/24580, WO 96/22997, WO 95/17423 and WO 95/17422 (all assigned to Novo Nordisk A/S); WO 96/15148 (Genentech Inc.); WO 97/22620 (Deghenghi); WO 02/32888, WO 02/32878, WO 00/49037, WO 00/10565 and WO 99/08699 (all assigned to Eli Lilly and Co.); WO 02/057241 and WO 02/056873 (both assigned to Bayer Corp.); and WO 01/85695, WO 00/54729 and WO 00/24398 (all assigned to Bristol-Myers Squibb Co.). The compounds are recommended for use in promoting the growth of food animals, and in humans for treating physiological or medical conditions characterised by a deficiency in growth hormone secretion, and medical conditions which are improved by the anabolic effects of growth hormone. In some of the above-listed disclosures, the list of treatable conditions includes AD.

The compound disclosed in the aforementioned US 5,767,124 has been the subject of a number of clinical trials in therapeutic fields unrelated to AD (see, for example, Murphy et al, *J. Bone Miner. Res.*, 14,

(1999), 1182-8; Chapman et al, *J. Clinical Endocrinology and Metabolism*, 81, (1996), 4249-57; *ibid.*, 82, (1997), 3455-63; and Svensson et al, *ibid.*, 83, (1998), 362-9).

According to the invention, there is provided a method of treatment or prevention of Alzheimer's disease comprising administering to a subject in need thereof a therapeutically effective amount of a growth hormone secretagogue (GHS) in combination with a therapeutically effective amount of at least one agent which modifies the production or processing of A $\beta$  in the brain, said at least one agent being selected from:

- (a) compounds which inhibit the secretion of A $\beta$ ;
- (b) compounds which selectively inhibit the secretion of the 1-42 isoform of A $\beta$ ;
- (c) compounds which inhibit the aggregation of A $\beta$  ; and
- (d) antibodies which selectively bind to A $\beta$ .

The invention further provides a method of treating, preventing or delaying the onset of dementia associated with Alzheimer's disease, cerebral amyloid angiopathy, multi-infarct dementia, dementia puglistica or Down syndrome comprising administering to a patient in need thereof a therapeutically effective amount of a growth hormone secretagogue in combination with a therapeutically effective amount of at least one agent as defined above which modifies the production or processing of A $\beta$  in the brain.

As used herein, the expression "in combination with" requires that therapeutically effective amounts of both a GHS and an agent which modifies the production or processing of A $\beta$  in the brain (hereinafter termed an "amyloid modifier") are administered to the subject, but places no restriction on the manner in which this is achieved. Thus, the two species may be combined in a single dosage form for simultaneous administration to the subject, or may be provided in separate dosage forms for simultaneous or sequential administration to the subject. Sequential administration may be close in time or remote in time, e.g. one species



administered in the morning and the other in the evening. The separate species may be administered at the same frequency or at different frequencies, e.g. one species once a day and the other two or more times a day. The separate species may be administered by the same route or by  
5 different routes, e.g. one species orally and the other parenterally, although oral administration of both species is preferred, where possible. When the amyloid modifier is an antibody, it will typically be administered parenterally and separately from the GHS.

According to a further aspect of the invention there is provided a  
10 pharmaceutical composition comprising, in a pharmaceutically acceptable carrier, a growth hormone secretagogue and an amyloid modifier selected from:

- (a) compounds which inhibit the secretion of  $A\beta$ ;
- (b) compounds which selectively inhibit the secretion of the 1-42  
15 isoform of  $A\beta$ ; and
- (c) compounds which inhibit the aggregation of  $A\beta$ .

The invention further provides the use, for the manufacture of a medicament for treatment or prevention of AD, of a growth hormone secretagogue and an amyloid modifier selected from:

- 20 (a) compounds which inhibit the secretion of  $A\beta$ ;
- (b) compounds which selectively inhibit the secretion of the 1-42 isoform of  $A\beta$ ;
- (c) compounds which inhibit the aggregation of  $A\beta$ .

The GHS and amyloid modifier act synergistically in reducing the  
25 accumulation of  $A\beta$  in the brain. Therefore, in a further aspect the invention provides a method for retarding, arresting or preventing the accumulation of  $A\beta$  in the brain comprising administering to a subject in need thereof a therapeutically effective amount of a growth hormone secretagogue in combination with a therapeutically effective amount of an  
30 amyloid modifier as defined above.

Because of the aforementioned synergistic interaction, it is possible to obtain a beneficial therapeutic effect from the administration of doses of the compounds in question that are smaller than would typically be employed for individual administration of the same compounds. For  
5 example, a compound which inhibits secretion of A $\beta$  (such as a  $\gamma$ -secretase inhibitor) may be dosed at a level which does not completely suppress the production of A $\beta$ , yet still exert a therapeutic effect comparable to full suppression thereof, as a result of co-administration of the GHS. This has the potential to prevent side-effects that might arise from the suppression  
10 of other activities, unconnected with A $\beta$  production, such as the notch signalling process.

Clearance of A $\beta$  from the brain following administration of the relevant compounds may be evidenced by an increase in the level of soluble A $\beta$  in the cerebrospinal fluid and/or the plasma. Alternatively (or  
15 additionally), imaging techniques such as magnetic resonance imaging, positron emission tomography, single photon emission computed tomography and multiphoton microscopy may be employed to monitor the extent of A $\beta$  deposition in the brain (see, for example, Bacskai *et al.*, *J. Cereb. Blood Flow Metab.*, **22** (2002), 1035-41).

20 In one embodiment of the invention, the GHS and amyloid modifier are administered to a patient suffering from AD, cerebral amyloid angiopathy, multi-infarct dementia, dementia pugilistica or Down syndrome, preferably AD.

In an alternative embodiment of the invention, the GHS and  
25 amyloid modifier are administered to a patient suffering from mild cognitive impairment or age-related cognitive decline. A favourable outcome of such treatment is prevention or delay of the onset of AD. Age-related cognitive decline and mild cognitive impairment (MCI) are conditions in which a memory deficit is present, but other diagnostic  
30 criteria for dementia are absent (Santacruz and Swagerty, *American Family Physician*, **63** (2001), 703-13). (See also "The ICD-10 Classification

of Mental and Behavioural Disorders", Geneva: World Health Organisation, 1992, 64-5). As used herein, "age-related cognitive decline" implies a decline of at least six months' duration in at least one of: memory and learning; attention and concentration; thinking; language; and  
5 visuospatial functioning and a score of more than one standard deviation below the norm on standardized neuropsychologic testing such as the MMSE. In particular, there may be a progressive decline in memory. In the more severe condition MCI, the degree of memory impairment is outside the range considered normal for the age of the patient but AD is  
10 not present. The differential diagnosis of MCI and mild AD is described by Petersen *et al.*, *Arch. Neurol.*, **56** (1999), 303-8.

Within this embodiment, the GHS and amyloid modifier are advantageously administered to patients who suffer impaired memory function but do not exhibit symptoms of dementia. Such impairment of  
15 memory function typically is not attributable to systemic or cerebral disease, such as stroke or metabolic disorders caused by pituitary dysfunction. Such patients may be in particular people aged 55 or over, especially people aged 60 or over, and preferably people aged 65 or over. Such patients may have normal patterns and levels of growth hormone  
20 secretion for their age. However, such patients may possess one or more additional risk factors for developing Alzheimer's disease. Such factors include a family history of the disease; a genetic predisposition to the disease; elevated serum cholesterol; and adult-onset diabetes mellitus.

In a particular embodiment of the invention, GHS and amyloid  
25 modifier are administered to a patient suffering from age-related cognitive decline or MCI who additionally possesses one or more risk factors for developing AD selected from: a family history of the disease; a genetic predisposition to the disease; elevated serum cholesterol; and adult-onset diabetes mellitus.

30 A genetic predisposition (especially towards early onset AD) can arise from point mutations in one or more of a number of genes, including

the APP, presenilin-1 and presenilin-2 genes. Also, subjects who are homozygous for the  $\epsilon 4$  isoform of the apolipoprotein E gene are at greater risk of developing AD.

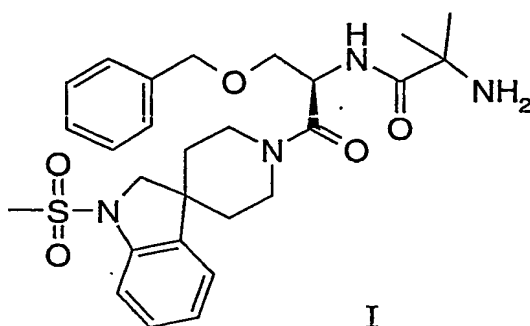
The patient's degree of cognitive decline or impairment is advantageously assessed at regular intervals before, during and/or after a course of treatment in accordance with the invention, so that changes therein may be detected, e.g. the slowing or halting of cognitive decline. A variety of neuropsychological tests are known in the art for this purpose, such as the Mini-Mental State Examination (MMSE) with norms adjusted for age and education (Folstein *et al.*, *J. Psych. Res.*, **12** (1975), 196-198, Anthony *et al.*, *Psychological Med.*, **12** (1982), 397-408; Cockrell *et al.*, *Psychopharmacology*, **24** (1988), 689-692; Crum *et al.*, *J. Am. Med. Assoc'n.* **18** (1993), 2386-2391). The MMSE is a brief, quantitative measure of cognitive status in adults. It can be used to screen for cognitive decline or impairment, to estimate the severity of cognitive decline or impairment at a given point in time, to follow the course of cognitive changes in an individual over time, and to document an individual's response to treatment. Another suitable test is the Alzheimer Disease Assessment Scale (ADAS), in particular the cognitive element thereof (ADAS-cog) (See Rosen *et al.*, *Am. J. Psychiatry*, **141** (1984), 1356-64).

The invention further provides a kit comprising a first medicament comprising a GHS and a second medicament comprising an amyloid modifier together with instructions for administering said medicaments sequentially or simultaneously to a patient suffering from AD, age-related cognitive decline, MCI, cerebral amyloid angiopathy, multi-infarct dementia, dementia pugilistica or Down syndrome.

The GHS used in the invention may be any compound which has the property of stimulating or enhancing secretion of endogenous growth hormone when administered to a subject, for example any of the compounds disclosed in the patents and patent applications listed above.

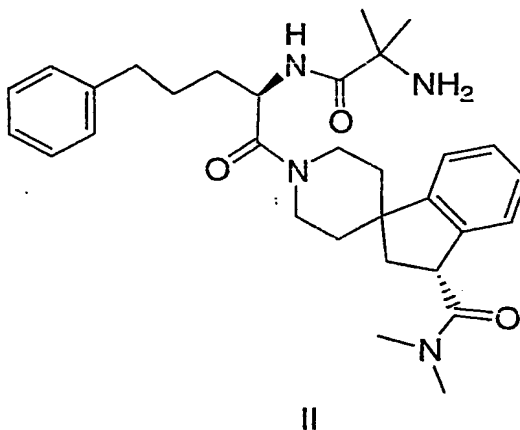
However, preference is given to compounds which are suitable for oral administration.

A first class of GHSs suitable for use in the invention is that disclosed in WO 94/13696, in particular the subset thereof disclosed in EP 0615977B, the disclosure of which is incorporated herein by reference. Preferred examples of GHSs within this class include the compound of formula I:



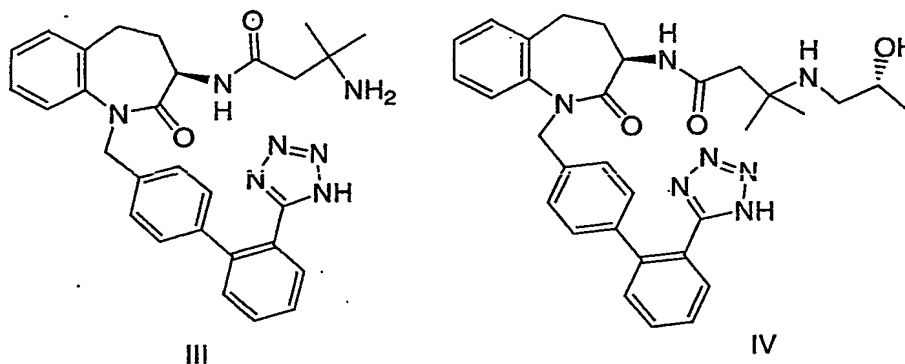
named as N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethoxy)ethyl]-2-amino-2-methylpropanamide, and pharmaceutically acceptable salts thereof, in particular the methanesulfonate salt thereof, which may be prepared as described in US 5,767,124.

A second class of GHSs suitable for use in the invention is that disclosed in US 5,578,593, the disclosure of which is incorporated herein by reference. Preferred example of GHSs within this class include the compound of formula II:



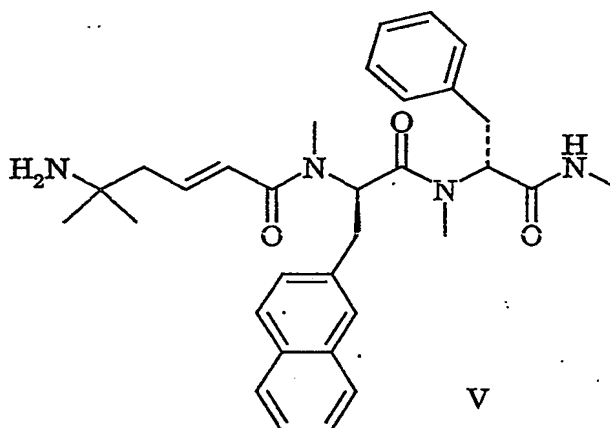
and pharmaceutically acceptable salts thereof, which may be prepared as described in US 5,578,593.

A third class of GHSs suitable for use in the invention is that disclosed in WO 92/16524, the disclosure of which is incorporated herein  
5 by reference. Preferred example of GHSs within this class include the compounds of formulae III and IV:



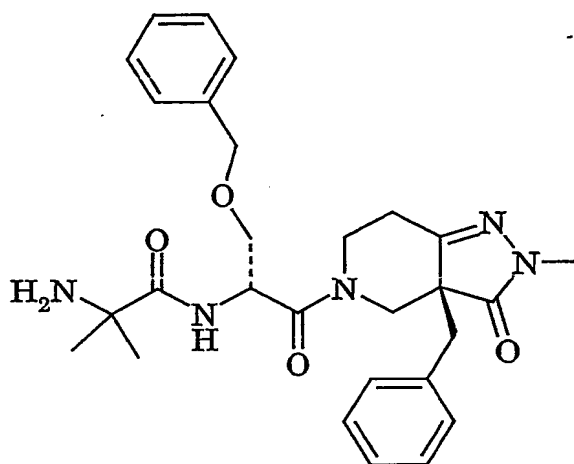
and pharmaceutically acceptable salts thereof, in particular the trifluoroacetate salts thereof, which may be prepared as described in WO  
10 92/16524.

A fourth class of GHSs suitable for use in the invention is that disclosed in WO 97/23508, the disclosure of which is incorporated herein by reference. Preferred examples of GHSs within this class include the compound of formula V, also known as NN703:



15 and pharmaceutically acceptable salts thereof, which may be prepared as described in WO 99/64456.

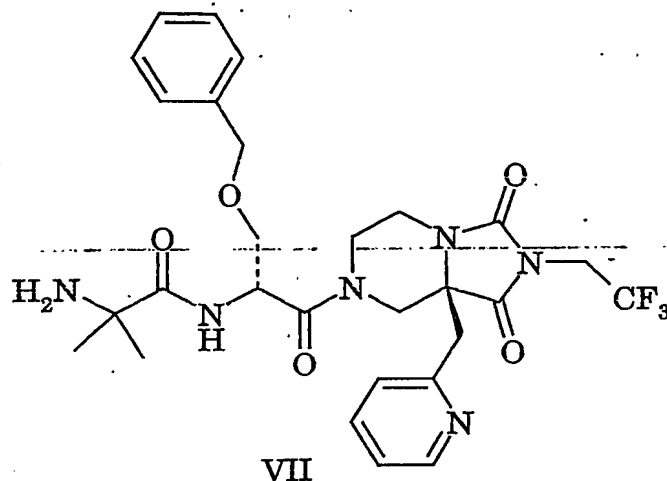
A fifth class of GHSs suitable for use in the invention is that disclosed in WO 97/24369, the disclosure of which is incorporated herein by reference. Preferred examples of GHSs within this class include the compound of formula VI:



VI

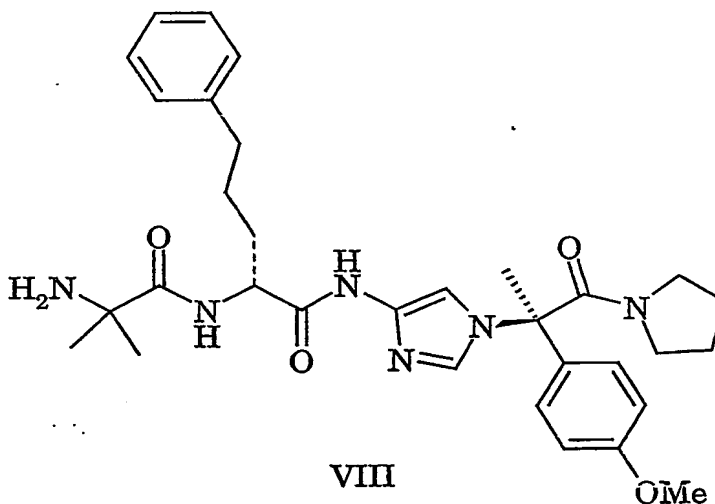
5 named as 2-amino-*N*-[2-(3a-(*R*)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-*c*]pyridin-5-yl)-1-(*R*)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide, and pharmaceutically acceptable salts thereof, in particular the *L*-tartrate salt, also known as capromorelin, which may be  
10 prepared as described in WO 97/24369 and in Carpino et al, *Bioorg. Med. Chem.*, **11** (2003), 581-90.

A sixth class of GHSs suitable for use in the invention is that disclosed in WO 98/58947, the disclosure of which is incorporated herein by reference. Preferred examples of GHSs within this class include the  
15 compound of formula VII:



and pharmaceutically acceptable salts thereof, which may be prepared as described in WO 98/58947.

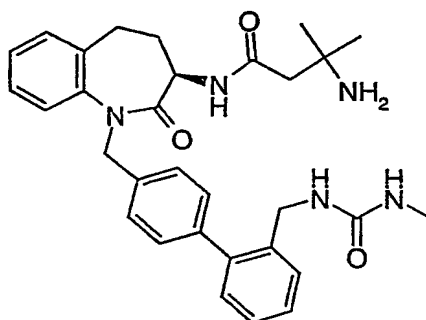
A seventh class of GHSs suitable for use in the invention is that disclosed in WO 99/08699, the disclosure of which is incorporated herein by reference. Preferred examples of GHSs within this class include the compound of formula VIII:



and pharmaceutically acceptable salts thereof, which may be prepared as described in WO 99/08699 and WO 02/32878.

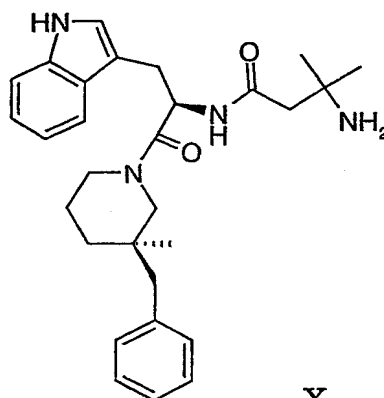
Further GHSs suitable for use in the invention include the compound of formula IX;





IX

and pharmaceutically acceptable salts thereof, which may be prepared as described in De Vita et al, *J.Med.Chem.*, 41 (1998), 1716-28, and the compound of formula X:



X

5

and pharmaceutically acceptable salts thereof, which may be prepared as described in Yang et al, *J.Med.Chem.*, 41 (1998), 2439-41.

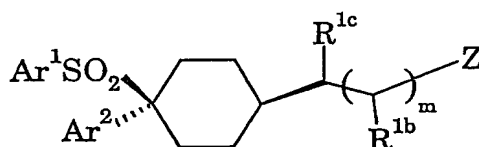
Preferably, the GHS is selected from the compounds of formulae I, II, V, VI, VIII and IX depicted above, and their pharmaceutically acceptable salts. Most preferably, the GHS used in the invention is the methanesulfonate salt of the compound of formula I which is in one of the polymorphic forms described in US 5,767,124.

In one embodiment of the invention, the amyloid modifier is a compound which inhibits the secretion of A $\beta$ , for example an inhibitor of  $\gamma$ -secretase (such as those disclosed in WO 01/53255, WO 01/66564, WO 01/70677, WO 01/90084, WO 01/77144, WO 02/30912, WO 02/36555, WO 02/081435, WO 02/081433, WO 03/018543, WO 03/013506, WO 03/013527 and WO 03/014075), or a  $\beta$ -secretase inhibitor (such as those disclosed in

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WO 03/037325, WO 03/030886, WO 03/006013, WO 03/006021, WO 03/006423, WO 03/006453, WO 02/002122, WO 01/70672, WO 02/02505, WO 02/02506, WO 02/02512, WO 02/02520, WO 02/098849 and WO 02/100820), or any other compound which inhibits the formation or release of A $\beta$ , including those disclosed in WO 98/28268, WO 02/47671, WO 99/67221, WO 01/34639, WO 01/34571, WO 00/07995, WO 00/38618, WO 01/92235, WO 01/77086, WO 01/74784, WO 01/74796, WO 01/74783, WO 01/60826, WO 01/19797, WO 01/27108, WO 01/27091, WO 00/50391, WO 02/057252, US 2002/0025955 and US2002/0022621, and also including GSK-3 inhibitors, particularly GSK-3 $\alpha$  inhibitors, such as lithium, as disclosed in Phiel et al, *Nature*, 423 (2003), 435-9.

Within this embodiment, the amyloid modifier is advantageously a  $\gamma$ -secretase inhibitor, preferred examples of which include a compound of formula XI:



XI

wherein:

m is 0 or 1;

Z represents halogen, CN, NO<sub>2</sub>, N<sub>3</sub>, CF<sub>3</sub>, OR<sup>2a</sup>, N(R<sup>2a</sup>)<sub>2</sub>, CO<sub>2</sub>R<sup>2a</sup>, OCOR<sup>2a</sup>, COR<sup>2a</sup>, CON(R<sup>2a</sup>)<sub>2</sub>, OCON(R<sup>2a</sup>)<sub>2</sub>, CONR<sup>2a</sup>(OR<sup>2a</sup>), CON(R<sup>2a</sup>)N(R<sup>2a</sup>)<sub>2</sub>, CONHC(=NOH)R<sup>2a</sup>, heterocyclyl, phenyl or heteroaryl, said heterocyclyl, phenyl or heteroaryl bearing 0-3 substituents selected from halogen, CN, NO<sub>2</sub>, CF<sub>3</sub>, OR<sup>2a</sup>, N(R<sup>2a</sup>)<sub>2</sub>, CO<sub>2</sub>R<sup>2a</sup>, COR<sup>2a</sup>, CON(R<sup>2a</sup>)<sub>2</sub> and C<sub>1-4</sub>alkyl;

R<sup>1b</sup> represents H, C<sub>1-4</sub>alkyl or OH;

R<sup>1c</sup> represents H or C<sub>1-4</sub>alkyl;

with the proviso that when m is 1, R<sup>1b</sup> and R<sup>1c</sup> do not both represent C<sub>1-4</sub>alkyl;

Ar<sup>1</sup> represents C<sub>6-10</sub>aryl or heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CN, NO<sub>2</sub>, CF<sub>3</sub>, OH,

OCF<sub>3</sub>, C<sub>1-4</sub>alkoxy or C<sub>1-4</sub>alkyl which optionally bears a substituent selected from halogen, CN, NO<sub>2</sub>, CF<sub>3</sub>, OH and C<sub>1-4</sub>alkoxy;

Ar<sup>2</sup> represents C<sub>6-10</sub>aryl or heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CN, NO<sub>2</sub>, CF<sub>3</sub>, OH,  
5 OCF<sub>3</sub>, C<sub>1-4</sub>alkoxy or C<sub>1-4</sub>alkyl which optionally bears a substituent selected from halogen, CN, NO<sub>2</sub>, CF<sub>3</sub>, OH and C<sub>1-4</sub>alkoxy;

R<sup>2a</sup> represents H, C<sub>1-6</sub>alkyl, C<sub>3-6</sub>cycloalkyl, C<sub>3-6</sub>cycloalkylC<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, any of which optionally bears a substituent selected from halogen, CN, NO<sub>2</sub>, CF<sub>3</sub>, OR<sup>2b</sup>, CO<sub>2</sub>R<sup>2b</sup>, N(R<sup>2b</sup>)<sub>2</sub>, CON(R<sup>2b</sup>)<sub>2</sub>, Ar and COAr; or  
10 R<sup>2a</sup> represents Ar; or two R<sup>2a</sup> groups together with a nitrogen atom to which they are mutually attached may complete an N-heterocyclyl group bearing 0-4 substituents independently selected from =O, =S, halogen, C<sub>1-4</sub>alkyl, CN, NO<sub>2</sub>, CF<sub>3</sub>, OH, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkoxycarbonyl, CO<sub>2</sub>H, amino, C<sub>1-4</sub>alkylamino, di(C<sub>1-4</sub>alkyl)amino, carbamoyl, Ar and COAr;

15 R<sup>2b</sup> represents H, C<sub>1-6</sub>alkyl, C<sub>3-6</sub>cycloalkyl, C<sub>3-6</sub>cycloalkylC<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, any of which optionally bears a substituent selected from halogen, CN, NO<sub>2</sub>, CF<sub>3</sub>, OH, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkoxycarbonyl, CO<sub>2</sub>H, amino, C<sub>1-4</sub>alkylamino, di(C<sub>1-4</sub>alkyl)amino, carbamoyl, Ar and COAr; or R<sup>2b</sup> represents Ar; or two R<sup>2b</sup> groups together with a nitrogen atom to which  
20 they are mutually attached may complete an N-heterocyclyl group bearing 0-4 substituents independently selected from =O, =S, halogen, C<sub>1-4</sub>alkyl, CN, NO<sub>2</sub>, CF<sub>3</sub>, OH, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkoxycarbonyl, CO<sub>2</sub>H, amino, C<sub>1-4</sub>alkylamino, di(C<sub>1-4</sub>alkyl)amino, carbamoyl, Ar and COAr;

Ar represents phenyl or heteroaryl bearing 0-3 substituents selected  
25 from halogen, C<sub>1-4</sub>alkyl, CN, NO<sub>2</sub>, CF<sub>3</sub>, OH, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkoxycarbonyl, amino, C<sub>1-4</sub>alkylamino, di(C<sub>1-4</sub>alkyl)amino, carbamoyl, C<sub>1-4</sub>alkylcarbamoyl and di(C<sub>1-4</sub>alkyl)carbamoyl;

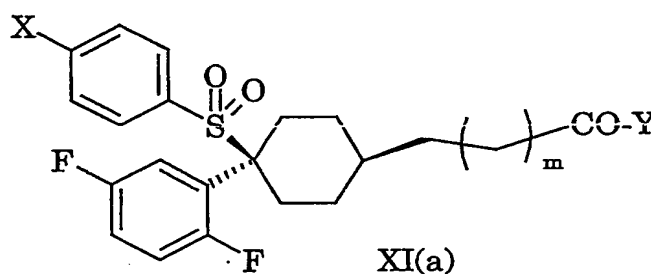
"heterocyclyl" at every occurrence thereof means a cyclic or polycyclic system of up to 10 ring atoms selected from C, N, O and S,  
30 wherein none of the constituent rings is aromatic and wherein at least one ring atom is other than C; and

"heteroaryl" at every occurrence thereof means a cyclic or polycyclic system of up to 10 ring atoms selected from C, N, O and S, wherein at least one of the constituent rings is aromatic and wherein at least one ring atom of said aromatic ring is other than C;

5 or a pharmaceutically acceptable salt thereof.

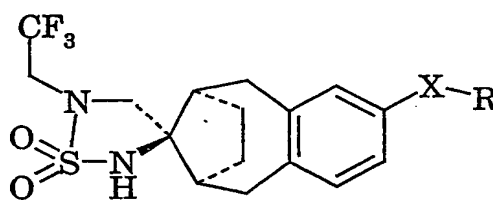
Such compounds may be prepared as described in WO 03/018543.

Preferred examples include those defined by formula XIa:



10 and the pharmaceutically acceptable salts thereof, wherein m is 0 or 1, X is Cl or CF<sub>3</sub>, and Y is OH, OC<sub>1-6</sub>alkyl, NH<sub>2</sub> or NHC<sub>1-6</sub>alkyl. Particular examples include those in which m is 1 and Y is OH (or the sodium salts thereof), and those in which m is 0 and Y is NH<sub>2</sub> or NHC<sub>1-6</sub>alkyl.

Another preferred class of  $\gamma$ -secretase inhibitors for use in this embodiment of the invention is that defined by formula XII:



XII

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wherein X is a bivalent pyrazole, imidazole, triazole, oxazole, isoxazole, thiazole, isothiazole, thiadiazole or 1,3,4-oxadiazole residue optionally bearing a hydrocarbon substituent comprising 1-5 carbon atoms which is optionally substituted with up to 3 halogen atoms; and

20 R is selected from:

(i) CF<sub>3</sub> or a non-aromatic hydrocarbon group of up to 10 carbon atoms, optionally substituted with halogen, CF<sub>3</sub>, CHF<sub>2</sub>, CN, OH, CO<sub>2</sub>H, C<sub>2-6</sub>acyl, C<sub>1-4</sub>alkoxy or C<sub>1-4</sub>alkoxycarbonyl;

(ii) a non-aromatic heterocyclic group comprising up to 7 ring atoms of which up to 3 are chosen from N, O and S and the remainder are carbon, bearing 0-3 substituents independently selected from oxo, halogen, CN, C<sub>1-6</sub>alkyl, OH, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, C<sub>2-6</sub>acyl, CO<sub>2</sub>H, C<sub>1-4</sub>alkoxy and

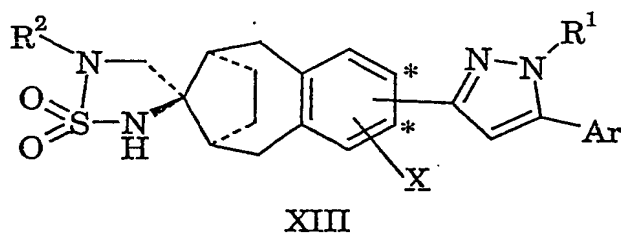
5 C<sub>1-4</sub>alkoxycarbonyl;

(iii) phenyl or 6-membered heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, NO<sub>2</sub>, CN, OCF<sub>3</sub>, C<sub>1-6</sub>alkyl and C<sub>1-6</sub>alkoxy; and

(iv) N(R<sup>a</sup>)<sub>2</sub> where each R<sup>a</sup> independently represents H or C<sub>1-6</sub>alkyl which is optionally substituted with halogen, CF<sub>3</sub>, CHF<sub>2</sub>, CN, OH, CO<sub>2</sub>H, C<sub>2-6</sub>acyl, C<sub>1-4</sub>alkoxy or C<sub>1-4</sub>alkoxycarbonyl; or a pharmaceutically acceptable salt thereof.

X is very aptly 5-substituted-thiazol-2-yl, 5-substituted-4-methylthiazol-2-yl, 5-substituted-1-methylpyrazol-3-yl, 1-substituted-15 imidazol-4-yl or 1-substituted-1,2,4-triazol-3-yl. Preferably, R represents optionally-substituted phenyl or heteroaryl such as phenyl, monohalophenyl, dihalophenyl, trihalophenyl, cyanophenyl, methylphenyl, methoxyphenyl, trifluoromethylphenyl, trifluoromethoxyphenyl, pyridyl, monohalopyridyl and trifluoromethylpyridyl, wherein "halo" refers to 20 fluoro or chloro. Particularly preferred identities of R-X- include 5-(4-fluorophenyl)-1-methylpyrazol-3-yl, 5-(4-chlorophenyl)-1-methylpyrazol-3-yl and 1-(4-fluorophenyl)imidazol-4-yl. Such compounds may be prepared by methods similar to those disclosed in WO 02/36555.

Another preferred class of  $\gamma$ -secretase inhibitors for use in this 25 embodiment of the invention is that defined by formula XIII:



wherein the pyrazole group is attached at one of the positions indicated by an asterisk and X is attached at a position adjacent thereto;

X represents H, OH, C<sub>1-4</sub>alkoxy, Cl or F;

Ar represents phenyl or 6-membered heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, NO<sub>2</sub>, CN, OCF<sub>3</sub>, C<sub>1-6</sub>alkyl and C<sub>1-6</sub>alkoxy;

R<sup>1</sup> represents a hydrocarbon group of 1-5 carbon atoms which is optionally substituted with up to 3 halogen atoms; and

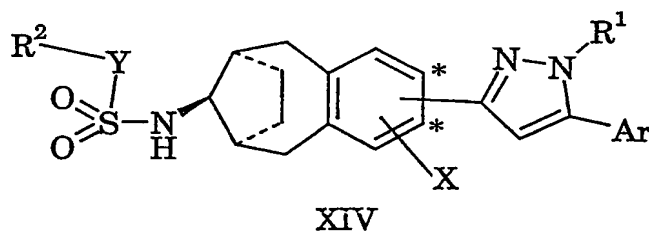
R<sup>2</sup> represents H or a hydrocarbon group of 1-10 carbon atoms which is optionally substituted with up to 3 halogen atoms;

provided that when X is H, R<sup>2</sup> does not represent 2,2,2-trifluoroethyl;

or a pharmaceutically acceptable salt thereof.

Preferred examples of compounds of formula XIII include those in which Ar is 4-fluorophenyl, R<sup>1</sup> is methyl, X is H and R<sup>2</sup> is benzyl, n-propyl, 2,2-dimethylpropyl, n-butyl, isopropyl, t-butyl, 3,3,3-trifluoropropyl, allyl, cyclobutyl or cyclopropylmethyl. Such compounds may be prepared by methods similar to those disclosed in WO 02/36555.

Another preferred class of  $\gamma$ -secretase inhibitors for use in this embodiment of the invention is that defined by formula XIV:



wherein the pyrazole group is attached at one of the positions indicated by an asterisk and X is attached at a position adjacent thereto;

X represents H, OH, C<sub>1-4</sub>alkoxy, Cl or F;

Y represents a bond, O or NR<sup>3</sup>;

Ar represents phenyl or 6-membered heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, NO<sub>2</sub>, CN, OCF<sub>3</sub>, C<sub>1-6</sub>alkyl and C<sub>1-6</sub>alkoxy;

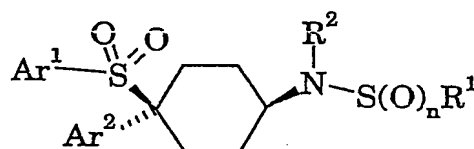
R<sup>1</sup> represents a hydrocarbon group of 1-5 carbon atoms which is optionally substituted with up to 3 halogen atoms; and

R<sup>2</sup> represents a hydrocarbon group of 1-10 carbon atoms which is optionally substituted with up to 3 halogen atoms, or heteroaryl of 5 or 6 ring atoms optionally bearing up to 3 substituents independently selected from halogen, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, NO<sub>2</sub>, CN, OCF<sub>3</sub>, C<sub>1-6</sub>alkyl and C<sub>1-6</sub>alkoxy; or when Y represents NR<sup>3</sup>, R<sup>2</sup> and R<sup>3</sup> together may complete a heterocyclic ring of up to 6 members which optionally bears up to 3 substituents independently selected from halogen, CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, NO<sub>2</sub>, CN, OCF<sub>3</sub>, C<sub>1-6</sub>alkyl and C<sub>1-6</sub>alkoxy;

R<sup>3</sup> represents H or C<sub>1-4</sub>alkyl, or together with R<sup>2</sup> completes a heterocyclic ring as defined above; or a pharmaceutically acceptable salt thereof.

Preferred examples of compounds of formula XIV include those in which Ar is 4-fluorophenyl, R<sup>1</sup> is methyl, X is H, and either Y is a bond and R<sup>2</sup> is n-butyl, 4-fluorophenyl, 5-chloro-2-thienyl, 5-isothiazolyl, 6-chloropyridin-3-yl or 2-thienyl, or Y is NR<sup>3</sup> and NR<sup>2</sup>R<sup>3</sup> is cyclobutylamino, 2,2,2-trifluoroethylamino, n-propylamino, N-methyl-n-propylamino, dimethylamino, pyrrolidin-1-yl or 4-(trifluoromethyl)piperidin-1-yl.

Another preferred class of  $\gamma$ -secretase inhibitors for use in this embodiment of the invention is that defined by formula XV:



XV

wherein n is 1 or 2;

R<sup>1</sup> represents CF<sub>3</sub> or C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>3-9</sub>cycloalkyl or C<sub>3-6</sub>cycloalkylC<sub>1-6</sub>alkyl, any of which may bear up to 2 substituents

selected from halogen, CN, CF<sub>3</sub>, OR<sup>3</sup>, COR<sup>3</sup>, CO<sub>2</sub>R<sup>3</sup>, OCOR<sup>4</sup>, SO<sub>2</sub>R<sup>4</sup>, N(R<sup>5</sup>)<sub>2</sub>, and CON(R<sup>5</sup>)<sub>2</sub>,

or R<sup>1</sup> represents aryl, arylC<sub>1-6</sub>alkyl, C-heterocyclyl or C-heterocyclylC<sub>1-6</sub>alkyl;

5 R<sup>2</sup> represents H or C<sub>1-4</sub>alkyl;

R<sup>3</sup> represents H, C<sub>1-4</sub>alkyl, phenyl or heteroaryl;

R<sup>4</sup> represents C<sub>1-4</sub>alkyl, phenyl or heteroaryl;

R<sup>5</sup> represents H or C<sub>1-4</sub>alkyl, or two R<sup>5</sup> groups together with a nitrogen atom to which they are mutually attached complete an azetidine, pyrrolidine, piperidine, morpholine, thiomorpholine or thiomorpholine-1,1-dioxide ring;

Ar<sup>1</sup> and Ar<sup>2</sup> independently represent phenyl or heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CN, NO<sub>2</sub>, CF<sub>3</sub>, CHF<sub>2</sub>, OH, OCF<sub>3</sub>, CHO, CH=NOH, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkoxycarbonyl, C<sub>2-6</sub>acyl, C<sub>2-6</sub>alkenyl and C<sub>1-4</sub>alkyl which optionally bears a substituent selected from halogen, CN, NO<sub>2</sub>, CF<sub>3</sub>, OH and C<sub>1-4</sub>alkoxy;

"aryl" at every occurrence thereof refers to phenyl or heteroaryl which optionally bear up to 3 substituents selected from halogen, CN, NO<sub>2</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, OR<sup>3</sup>, COR<sup>3</sup>, CO<sub>2</sub>R<sup>3</sup>, OCOR<sup>4</sup>, N(R<sup>5</sup>)<sub>2</sub>, CON(R<sup>5</sup>)<sub>2</sub> and optionally-substituted C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>2-6</sub>alkenyl or C<sub>2-6</sub>alkenyloxy wherein the substituent is selected from halogen, CN, CF<sub>3</sub>, phenyl, OR<sup>3</sup>, CO<sub>2</sub>R<sup>3</sup>, OCOR<sup>4</sup>, N(R<sup>5</sup>)<sub>2</sub> and CON(R<sup>5</sup>)<sub>2</sub>; and

"C-heterocyclyl" and "N-heterocyclyl" at every occurrence thereof refer respectively to a heterocyclic ring system bonded through carbon or nitrogen, said ring system being non-aromatic and comprising up to 10 atoms, at least one of which is O, N or S, and optionally bearing up to 3 substituents selected from oxo, halogen, CN, NO<sub>2</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, OR<sup>3</sup>, COR<sup>3</sup>, CO<sub>2</sub>R<sup>3</sup>, OCOR<sup>4</sup>, OSO<sub>2</sub>R<sup>4</sup>, N(R<sup>5</sup>)<sub>2</sub>, CON(R<sup>5</sup>)<sub>2</sub> and optionally-substituted phenyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>2-6</sub>alkenyl or C<sub>2-6</sub>alkenyloxy wherein the

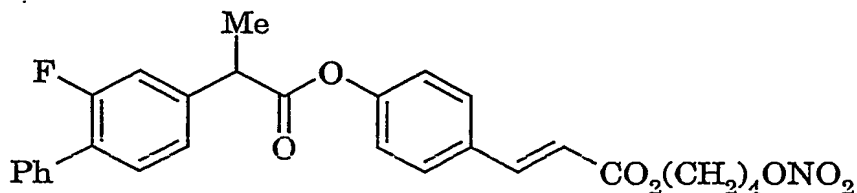


substituent is selected from halogen, CN, CF<sub>3</sub>, OR<sup>3</sup>, CO<sub>2</sub>R<sup>3</sup>, OCOR<sup>4</sup>, N(R<sup>5</sup>)<sub>2</sub> and CON(R<sup>5</sup>)<sub>2</sub>;

or a pharmaceutically acceptable salt thereof.

Preferred examples of compounds of formula XV include those in which R<sup>1</sup> is CF<sub>3</sub>, Ar<sup>2</sup> is 2,5-difluorophenyl and Ar<sup>1</sup> is 4-chlorophenyl, 4-trifluoromethylphenyl or 6-trifluoromethylpyridin-3-yl. Compounds of formula XV may be prepared by reaction of R<sup>1</sup>SO<sub>2</sub>Cl with the appropriate 4-aryl-4-arylsulphonylcyclohexylamine, the synthesis of said cyclohexylamines being described in WO 02/081435.

In a second embodiment of the invention, the amyloid modifier is a compound which selectively inhibits secretion of the 1-42 isoform of Aβ. Suitable examples of such compounds include the non-steroidal antiinflammatory drugs (NSAIDs) and their analogues disclosed in WO 01/78721 and US 2002/0128319, such as sulindac sulfide, flufenamic acid, ibuprofen, flurbiprofen, fenoprofen, mefenamic acid, indomethacin and (R)-flurbiprofen. A preferred example is (R)-flurbiprofen. Alternatively, an NSAID derivative capable of releasing nitric oxide may be employed (e.g. compounds as disclosed in WO 02/092072 and in Jantzen et al, *J. Neuroscience*, **22** (2002), 226-54). Preferred examples of NO-releasing compounds include the 4-nitrooxybutyl ester of flurbiprofen (made by NiCox and also known as HCT-1026) and the compound:



known as NCX-2216 (NiCox). As a further alternative within this embodiment, a compound which modulates the activity of PPARα and/or PPARδ (as disclosed in WO 02/100836) may be employed.

In a third embodiment of the invention, the amyloid modifier is a compound which inhibits the aggregation of Aβ. Suitable examples include chelating agents such as clioquinol (Gouras and Beal, *Neuron*, **30**

(2001), 641-2) and the compounds disclosed in WO 99/16741, in particular that known as DP-109 (Kalendarev et al, *J. Pharm. Biomed. Anal.*, 24 (2001), 967-75). Other inhibitors of A $\beta$  aggregation suitable for use in the invention include the compounds disclosed in WO 96/28471, WO 98/08868 and WO 00/052048, including the compound known as Apan<sup>TM</sup> (Praecis); WO 00/064420, WO 03/017994, WO 99/59571 and the compound known as Alzhemed<sup>TM</sup> (Neurochem); WO 00/149281 and the compositions known as PTI-777 and PTI-00703 (ProteoTech); WO 96/39834, WO 01/83425, WO 01/55093, WO 00/76988, WO 00/76987, WO 00/76969, WO 00/76489, WO 97/26919, WO 97/16194, and WO 97/16191.

In a fourth embodiment of the invention, the amyloid modifier is an antibody which binds selectively to A $\beta$ . Said antibody may be polyclonal or monoclonal, but is preferably monoclonal, and is preferably human or humanized. Preferably, the antibody is capable of sequestering soluble A $\beta$  from biological fluids, as described in WO 03/016466, WO 03/016467, WO 03/015691 and WO 01/62801. Suitable antibodies include humanized antibody 266 (described in WO 01/62801) and the modified version thereof described in WO 03/016466.

In a particular embodiment of the invention, the amyloid modifier is selected from:

- (a) compounds which inhibit the secretion of A $\beta$ ;
- (b) compounds which selectively inhibit the secretion of the 1-42 isoform of A $\beta$ ;
- (c) compounds which inhibit the aggregation of A $\beta$ .

Depending on whether they are to be administered together or separately, the GHS and amyloid modifier are typically supplied as single or multiple pharmaceutical compositions comprising the active species and a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or

suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. The principal active ingredient typically is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate and dicalcium phosphate, or gums, dispersing agents, suspending agents or surfactants such as sorbitan monooleate and poly(ethylene glycol), and other pharmaceutical diluents, e.g. water, to form a homogeneous preformulation composition containing one or both active species, or pharmaceutically acceptable salts thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active species is or are dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This preformulation composition is then subdivided into unit dosage forms of the type described above, generally containing from 0.01 to about 500 mg of the active species. Typical unit dosage forms contain from 0.05 to 100 mg, for example 0.05, 0.1, 0.5, 1, 2, 5, 10, 25, 50 or 100 mg, of the active species. Tablets or pills of the pharmaceutical composition(s) can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the pharmaceutical compositions useful in the present invention may be incorporated for administration orally or by injection include aqueous solutions, liquid- or gel-filled capsules,

suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

5     Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, poly(ethylene glycol), poly(vinylpyrrolidone) and gelatin.

10     Pharmaceutical compositions suitable for oral administration are preferred, except when the amyloid modifier is an antibody, in which case parenteral administration of the antibody is preferred, e.g. by subcutaneous, intravenous or intraperitoneal injection.

15     For treatment or prevention of AD, the GHS and amyloid modifier may be dosed at the levels which are effective for the original purposes of the separate compounds. Thus, the GHS will typically be dosed at levels known to provide increased secretion of endogenous growth hormone in a human subject, and the amyloid modifier at levels known to cause significant inhibition of the secretion of A $\beta$ , or of the 1-42 isoform thereof, or significant inhibition of the aggregation of A $\beta$ , or significant sequestration of soluble A $\beta$ , as appropriate. In many cases, these dosage  
20     levels are available from the published literature, but otherwise are readily determined by standard clinical methods. However, as explained above, it may be possible and advantageous to use a smaller dose of the amyloid modifier than would otherwise be indicated, in view of the synergistic interaction with the GHS.

25     The frequency of dosing of the relevant compounds (e.g. once, twice, three times or four times per day) may be selected according to the pharmacokinetic profiles of the compounds concerned.

30     In the case of the preferred GHS of formula I, doses of about 0.01 to 5.0 mg/kg per day, preferably about 0.05 to 2.5 mg/kg per day, more preferably about 0.1 to 1.0 mg/kg of body weight per day, may be

contemplated. In particular, a dose equivalent to 5mg, 10 mg or 25 mg of the free base may be administered orally once daily to a patient.

In the case of a compound which inhibits the secretion of A $\beta$ , the dosage may be adjusted so as to provide complete suppression of the secretion of A $\beta$ , or only partial suppression thereof, for example a 50% reduction in A $\beta$  secretion. In the case of a  $\gamma$ -secretase inhibitor of formula XI or XII above, daily oral doses of about 25 to 500mg per person are contemplated, in particular about 50 to 250mg per person.

In a further aspect, the invention provides a pharmaceutical composition comprising, in a pharmaceutically acceptable carrier, a compound of formula I or a pharmaceutically acceptable salt thereof and a compound of formula XI(a) or a pharmaceutically acceptable salt thereof. Preferably the compound of formula I is in the form of the methanesulfonate salt. Preferably, the pharmaceutical composition is in a unit dose form suitable for oral administration, such as a tablet or a capsule. In a particular embodiment, said unit dose form contains the equivalent of 5, 10 or 25 mg of the free base of formula I and the equivalent of from 50 to 250 mg of the compound of formula XI(a).

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